Evolution of human BCR-ABL1 lymphoblastic leukaemia-initiating cells.

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Public Summary:
Many tumours are composed of genetically diverse cells; however, little is known about how diversity evolves or the impact that diversity has on functional properties. Here, using xenografting and DNA copy number alteration (CNA) profiling of human BCR-ABL1 lymphoblastic leukaemia, we demonstrate that genetic diversity occurs in functionally defined leukaemia-initiating cells and that many diagnostic patient samples contain multiple genetically distinct leukaemia-initiating cell subclones. Reconstructing the subclonal genetic ancestry of several samples by CNA profiling demonstrated a branching multi-clonal evolution model of leukaemogenesis, rather than linear succession. For some patient samples, the predominant diagnostic clone repopulated xenografts, whereas in others it was outcompeted by minor subclones. Reconstitution with the predominant diagnosis clone was associated with more aggressive growth properties in xenografts, deletion of CDKN2A and CDKN2B, and a trend towards poorer patient outcome. Our findings link clonal diversity with leukaemia-initiating-cell function and underscore the importance of developing therapies that eradicate all intratumoral subclones.

Scientific Abstract:
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